Bone Health & Neutropenia

Mary Ann Bonilla, MD
St. Joseph's Regional Medical Center, NJ
New York Medical College

Linda A. DiMeglio, MD, MPH
Indiana University School of Medicine
Bone Health Basics

- Bones support your body and allow you to move and protect your organs from injury
- 3 major components
  - Collagen, a protein that gives bones a flexible framework
  - Calcium-phosphate mineral complexes make bones hard and strong
  - Living bone cells
Bone Growth & Remodeling

- Lifelong balance of bone resorption (removal) and bone formation (deposit)
- Replaces bone following injuries like fractures
- Responds to functional/mechanical demands of the body
- During growth, bone size increases, but bone mass or density also increases

*Nature Reviews Cancer* 5, 2005
The Surgeon General’s report on bone health and osteoporosis: What it means to you. NIH March 2012
Osteoporosis

- Normal bone looks like a sea sponge - thick interconnected plates separated by spaces
- **Osteoporosis** is condition marked by low bone mass and deterioration of bone tissue
- Leads to bone fragility
- Increased risk of fractures of the hip, spine and wrist

- "Silent disease"
  No symptoms until a fracture occurs
Testing for Osteoporosis

- **DEXA scan**
  - *dual energy x-ray absorptiometry.*
- Utilizes 2 beams of low radiation to distinguish bone from soft tissue
- Scan time ~15-20 min.
- Can detect osteoporosis before a fracture occurs
The T’s and Z’s

- **T score**
  - Value that compares bone mineral density to mean value in a young adult population (matched for sex and race)

- **Z score**
  - Value that compares bone mineral density to the mean value for patients of the same age/sex
Risk Factors for Osteoporosis
Factors that cannot be changed

- Gender  Women > Men
- Race  Caucasians & Asian origin > African-American
- Genetics  Family history
- Stature  Short, thin, or small body = smaller, thinner bones
- Age  Increase risk with age
Pre- vs. Post-Menopause

- Both fractures and low bone mass are less common in premenopausal women.
- Low bone mass, due to either inadequate peak bone mass acquisition and/or ongoing bone loss.
- Different guidelines for diagnosis and treatment
Drugs at Risk

- Aluminum-containing antacids
- Antiseizure medicines (only some) such as Dilantin® or Phenobarbital
- Aromatase inhibitors such as Arimidex®, Aromasin® and Femara®
- Cancer chemotherapeutic drugs
- Cyclosporine A and FK506 (Tacrolimus)
- Gonadotropin releasing hormone (GnRH) such as Lupron® and Zoladex®
- Heparin
- Lithium
- Medroxyprogesterone acetate for contraception (Depo-Provera®)
- Methotrexate
- Proton pump inhibitors (PPIs) such as Nexium®, Prevacid® and Prilosec®
- Selective serotonin reuptake inhibitors (SSRIs) such as Lexapro®, Prozac® and Zoloft®
- **Steroids (glucocorticoids) such as cortisone and prednisone**
- Tamoxifen® (premenopausal use)
- Thiazolidinediones such as Actos® and Avandia®
- Thyroid hormones in excess
Diseases at Risk

• Autoimmune
  - Anklyosing spondylitis
  - Multiple Sclerosis
• Gastrointestinal Disorders
  - Celiac Disease
  - Inflammatory Bowel Disease (IBD)
  - Weight Loss Surgery.
  - Gastrectomy
  - Gastrointestinal bypass procedures
• Endocrine Disorders
  - Diabetes
  - Hyperparathyroidism
  - Hyperthyroidism
  - Cushing’s syndrome
  - Low estrogen levels.
  - Premature Menopause
  - Low Testosterone

• Blood Disorders
  - **Severe Chronic Neutropenia**
  - Sickle Cell Disease
  - Thalassemia
• Nervous System Disorders
  - Spinal cord injuries
• Mental Illness
  - Depression
  - Eating Disorders
• Other Diseases and Conditions
  - AIDS/HIV
  - Chronic obstructive pulmonary disease (COPD)
  - Kidney disease
Neutropenia & Low Bone Mass

- **Chronic Idiopathic Neutropenia**
  - Low BMD in 60% of persons
  - Related to higher levels of bone resorption cytokines (IL-1β and TNF-α) causing higher bone turnover

- **Severe Chronic Neutropenia (SCN)**
  - Low BMD in 48% of persons, half of whom had pathologic fractures and/or back pain
Possible Causes of Bone Loss

- Recurrent infections
- Decreased physical activity
- Poor nutrition
- Primary bone marrow problem
- Medications
- SCN treatment: G-CSF
Does G-CSF Cause Osteoporosis?

- YES

- G-CSF
  - can lead to bone loss in animal studies
  - causes production of a chemicals (cytokine IL-1) associated with osteoporosis
  - pushes cells to become monocytes/macrophages rather than bone forming cells (osteoblasts)
What cells build and break down bone?

G-CSF stimulates osteoclasts during short term administration.
Worsening of spine x-rays during G-CSF administration
Does G-CSF cause osteoporosis?

• NO

• Low bone mass and vertebral fractures were seen prior to starting G-CSF in SCN pts.

• No relationship between total amount of G-CSF given and osteoporosis development
How common is Osteoporosis in SCN?
Data from the SCN registry

<table>
<thead>
<tr>
<th>Condition</th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>46</td>
<td>11</td>
<td>57</td>
</tr>
<tr>
<td>Congenital</td>
<td>17</td>
<td>23</td>
<td>40</td>
</tr>
<tr>
<td>Cyclic</td>
<td>21</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>87</strong></td>
<td><strong>41</strong></td>
<td><strong>128</strong></td>
</tr>
<tr>
<td><strong>Under 18</strong></td>
<td>21%</td>
<td>54%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Data presented at 2010 American Society for Hematology
RESULTS: BMDs were low.

- **Children:**
  - mean BMD z-score was -1.0 ± 1.1,
  - with 17.5% BMDs that were < -2.0

- **Adults:**
  - mean BMD t-score was -1.1 ± 1.4,
  - 46% of adults = osteopenia (≤ -1.0)
  - 9% = osteoporosis (< -2.5)

- BMDs lowest in congenital < cyclic
- Lower in pts on longer G-CSF therapy
What to Do?

• How to screen for low bone mass?
• Can we prevent osteoporosis in persons with SCN?
• Can we treat osteoporosis once recognized?
Osteoporosis → Fractures

- It is easier to prevent osteoporosis than to treat it once it has developed.
- Make the diagnosis as early as possible
Prevention:
Factors that can be changed

• Osteoporosis prevention should begin in childhood
• Bone mass acquired during childhood & adolescence is our natural protection, “Peak mass”
Factors that can be changed

- Diet
  - adequate calcium, phosphate, Vitamin D
- Exercise
- Lifestyle
- Estrogen levels
- Drugs
# Good-for-Your-Bones Foods

<table>
<thead>
<tr>
<th>Category</th>
<th>Foods</th>
<th>Nutrient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dairy</strong></td>
<td>milk, yogurt and cheese. Some dairy products are fortified with Vitamin D.</td>
<td>Calcium</td>
</tr>
<tr>
<td><strong>Fish</strong></td>
<td>Canned sardines and salmon (with bones)</td>
<td>Calcium</td>
</tr>
<tr>
<td></td>
<td>Fatty varieties such as salmon, mackerel, tuna and sardines</td>
<td>Vitamin D</td>
</tr>
<tr>
<td><strong>Fruits and vegetables</strong></td>
<td>Collard greens, turnip greens, kale, okra, Chinese cabbage, dandelion greens, mustard greens and broccoli</td>
<td>Calcium</td>
</tr>
<tr>
<td></td>
<td>Spinach, beet greens, okra, tomato products, artichokes, plantains, potatoes, sweet potatoes, collard greens and raisins.</td>
<td>Magnesium</td>
</tr>
<tr>
<td><strong>Dairy, meats, nuts, tofu, beans, “Coke”</strong></td>
<td>High in western diet</td>
<td>Phosphate</td>
</tr>
</tbody>
</table>
## Calcium: Adequate Intake

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>Age</th>
<th>Males &amp; Females (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>0-6 months</td>
<td>210</td>
</tr>
<tr>
<td>Infants</td>
<td>7-12 months</td>
<td>270</td>
</tr>
<tr>
<td>Children</td>
<td>1-3 years</td>
<td>500</td>
</tr>
<tr>
<td>Children</td>
<td>4-8 years</td>
<td>800</td>
</tr>
<tr>
<td>Children &amp; Adolescents</td>
<td>9-19 years</td>
<td>1,300</td>
</tr>
<tr>
<td>Adults</td>
<td>19-50 years</td>
<td>1,000</td>
</tr>
<tr>
<td>Adults</td>
<td>51 years and older</td>
<td>1,200</td>
</tr>
</tbody>
</table>
Vitamin D

• Important for bone mineralization
  - Gut effects
    • Increases calcium absorption
    • Increases phosphate absorption
  - Bone Effects
    • Increases bone resorption
    • Facilitates bone formation
  - Source
    • Fortified Milk
    • Sun
## Vitamin D

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>Age</th>
<th>Males &amp; Females mcg/day (IU/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>Birth – 1 year</td>
<td>10 mcg (400 IU)</td>
</tr>
<tr>
<td>Children Adolescents Adults</td>
<td>1 year and older</td>
<td>15 mcg (600 IU)</td>
</tr>
</tbody>
</table>

Institute of Medicine, Food and Nutrition Board.  
*Dietary Reference Intakes for Calcium and Vitamin D.*  
Washington, DC: National Academy Press, 2010
Lifestyles

• Caffeine
  - Moderate intake-Coffee, tea and soft drinks (sodas)
  - decrease calcium absorption

• Alcohol.
  - Lead to bone loss
  - Limit alcohol to no more than 2 - 3 drinks per day.

Smoking
  - Prevents new bone deposition, ↓ bone mass
Exercises for osteoporosis

• **Weight-bearing**
  - Your feet and legs support your body’s weight
  - Walking, hiking, dancing, stair climbing
  - Best!
• **Resistance**
  - Working against the weight of another object
  - Free weights or weight machines, resistance tubing, water exercises

• **Flexibility**
  - Regular stretches, T'ai chi, Yoga
  - Improves balance to prevent falls
What Screening Should be Done?

- Bone density by DEXA
- How often for SCN pts? **No clear data**
  - At diagnosis
  - If Abnormal-yearly
  - If Normal, every 2 years
- Need to have measurements done on same machine
  - For Children - **important** to be at Center used to measuring kids
What Screening Should be Done?

• Blood tests
  - calcium, phosphorus, 25-vitamin D (stored form of D),
  - parathyroid hormone (looks for stress on system)

• Urine calcium to see if adequate calcium being absorbed
Medications

- Medications are available for the prevention and treatment of osteoporosis
- Decision should be reached between the family and their doctor after a careful evaluation
  - Must find MD experienced in treating osteoporosis in children
Medications

• Anti-resorptive
  - Bisphosphonates, calcitonin, denosumab, estrogen and estrogen agonists
  - Decrease bone loss

• Anabolic Drugs
  - Teriparatide, a form of parathyroid hormone
  - Increases the rate of bone formation
Do they work for SCN?

- Limited data - Appear effective

**FIGURE 2.** Lumbar spine BMD z score on follow-up. Start: initiation of bisphosphonates; stop: discontinuation of bisphosphonates.
Spine remodeling with pamidronate
Side effects of use

- Intravenous forms:
  - fever, musculoskeletal aches, vomiting (with first infusion only)
  - Low blood calcium levels
  - Eye inflammation

- Oral forms:
  - stomach upset, inflammation and erosion of esophagus, esophageal CA
  - Prevented by taking with 8 oz of water; upright > 30 min after
Resources

• The National Osteoporosis Foundation
  - www.nof.org

• Patient information: Osteoporosis prevention and treatment (Beyond the Basics) UpToDate.

• NIH Osteoporosis and Related Bone Diseases National resource center.
  - www.niams.nih.gov/Health_Info/bone/